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Signed M.S. Dawson

Dated 27 JAN 1997

Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference — EH/55438

2. Patent application number *(The Patent Office will fill in this p...)* — **9526150.9** — 21 DEC 1995

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

R.P. Scherer Corporation
2075 West Big Beaver Road
Troy, Michigan 48007-7060
United States of America

Patents ADP number *(if you know it)* 6553248CCC1

If the applicant is a corporate body, give the country/state of its incorporation — Delaware, United States of America

4. Title of the invention

OPHTHALMIC TREATMENT

5. Name of your agent *(if you have one)* — Lloyd Wise, Tregear & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Norman House
105-109 Strand
London WC2R 0AE

Patents ADP number *(if you know it)* — 117001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	5
Claim(s)	1
Abstract	
Drawing(s)	1

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Date 21/12/1995

Lloyd Wise, Tregear & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Esmond A. Hitchcock 0171 836 0986

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After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

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OPHTHALMIC TREATMENT

This invention relates to ophthalmic treatment and more particularly, to dosage forms useful in such treatment. The invention is concerned only with liquid treatment substances.

Ocular medication is most frequently administered as eye drop solutions. The typical volume of an eye drop has been found to range from 25 µl to 50 µl. Under normal conditions, in the open eye the human tear volume remains relatively constant at around 7 µl, with continuous drainage of tear fluid (via the nasolacrimal canal) being replaced by the tear glands. The tear volume can increase to about 30 µl before overflowing occurs and the excess fluid is lost either through the nasolacrimal duct or by spillage onto the cheek. Blinking reduces this maximal volume to say, 10 µl. Thus the addition of large volumes of liquid such as those presented in commercial eyedrops will result in the rapid elimination of the active agents from the eye with typically 80-90 % of an instilled drop being lost within one minute. Drug which drained through the highly vascular nasolacrimal duct can be absorbed into the systemic circulation as a bolus dose and therefore by-pass hepatic metabolism.

The recent use of ß-blocking agents in ophthalmology has highlighted the disadvantages associated with this rapid drainage process, with serious life threatening side-effects such as bradycardia, bronchospasm and even heart failure being induced in susceptible patients. In addition, research has also shown that the rate at which instilled solutions are drained from the eye varies directly with the instilled volume i.e.the larger the instilled volume, the more rapidly it is removed from the precorneal regions of the eye. These findings have led to the suggestion that a higher concentration of drug in

as small a volume as is practicable would be beneficial. In one study published in the American Journal of Ophthalmology 85, 1978 pp 225 to 229; Ocular bioavailability and systematic loss of topically applied ophthalmic drugs, by Thomas Patton and Michael Francoeur, it was reported that when using a 5 μl eye drop loaded with 26.1 μg of pilocarpine nitrate, the fraction of drug absorbed into the eye was 0.41 μg, leaving 25.7 μg available for potential systemic absorption. A similar calculation using a 25 μl drop loaded with 67.8 μg of pilocarpine nitrate, revealed that 0.36 μg had penetrated the eye, thus leaving 67.4 μg to be absorbed systemically. From this kind of study it can be concluded:

1. That an argument could be made for the use of smaller instilled volumes of eye drops than are normally delivered by most commercial ophthalmic droppers. Drainage loss would be minimised; contact time increased and hence the potential exists for improved drug activity.
2. Due to reduced drainage, less total volume of eye drop solution, and hence less drug need be used, therefore reducing the risk of systemic side-effects, whilst improving cost efficiency due to less wastage.

The research work referred to above is restricted to the use of ophthalmic solutions delivered as instillates. Surprisingly, we have found that the ocular bioavailability of ophthalmologically active compounds can be further enhanced by delivery to the eye in the form of a stream of droplets. Accordingly, the present invention provides a dosage form useful in ophthalmic treatment, comprising a stream of droplets of treatment fluid, each droplet having an ophthalmologically active compound in suspension or

solution, normally an aqueous solution.

While dosage forms according to the invention can be delivered vertically, under the force of gravity, preferred forms are also suitable for horizontal delivery. In such forms, each droplet is of a size sufficient to sustain its momentum in transmission from a delivery device to a target site. Preferably, the size of each droplet is sufficient to sustain its momentum along a substantially horizontal path of 5 cm in length from a discharge velocity of 5 to 25 m/sec from a delivery device. A typical minimum droplet diameter for these purposes is in the range 100 to 800 μm, preferably 200 to 400 μm.

The enhanced bioavailability of ophthalmologically active compounds in dosage forms according to the invention enables the use of even smaller total volumes of treatment fluid than proposed in the eye drop study discussed above. Typically, the total volume of treatment fluid in a dosage form according to the invention does not exceed 20 μl, preferably no greater than 10 μl, and most preferably, in the range 3 to 8 μl. The discharge of such a small volume from a delivery device at a suitable velocity to create the stream will normally beat the "blink response" and result in a high percentage of the active compound in the treatment fluid performing its intended function. In other words, the entire volume can be delivered to the chosen site on the eye before the patient blinks to disperse the received fluid.

Treatment fluid used in dosage forms of the invention can additionally contain excipients to prolong the residence time in the cul-de-sac (the conjunctival sac), and thereby further enhance bioavailability. Suitable excipients include viscosity modulators, polymers, gelling agents and thickeners.

The invention will now be described by way of example and with reference to the accompanying Figure

which illustrates the performance of three ocular treatments, one using dosage forms according to the present invention, and the other two using eye drops of the kind discussed above.

Six white New Zealand rabbits were administered with the following dosage regimen:

→ 25 µl of 1 % aqueous ephedrine hydrochloride solution (250 µg) via pipette

→ 5 µl of 5 % aqueous ephedrine hydrochloride solution (250 µg) via pipette

→ 5 µl of 5 % aqueous ephedrine hydrochloride solution (250 µg) in a stream of droplets of diameter in the range 200 to 400 µm.

Pupil diameter measurements were determined from photographs acquired using a Pentax ME super 35 mm camera fitted with a SMC Pentax 50 mm lens and a 2x converter. An aperture setting of 12, and a shutter speed of 1/15 was employed with a film speed of ISO 400 (Kodak Gold 400). The camera was held stationary on a tripod and positioned approximately 30-40 cm from the rabbits eye. Prior to each dosing period the animals were acclimatised to experimental conditions (constant light intensity, minimal distractions) for 20 min. The rabbits were placed in restraining boxes and settled before photographs and baseline pupil diameters were determined 5 min prior to dosing.

Pupillary diameters were determined from the developed colour prints (6 x 4) using an electronic micrometer (Digimatic Caliper, Mitutoyo Corp., Japan). Absolute pupil diameters were established by comparing the pupil diameter with a scale of known magnitude placed next to and in the same plane as the pupil prior to photography. The maximum response ratio (RR_{max}) for pupil dilation was then calculated from the photographs using the following relationship:

(RR_{max}) = (pupil diameter time t - average pupil diameter

time 0) / average pupil diameter time 0.

Results

The RR_{max} values for the varying dosage regimens are plotted in the Figure in relation to time. It can be seen that the mydriatic response obtained from the 5 μl ocular droplet dosage from was more pronounced and maintained over a longer duration compared to both instillates; in terms of RR_{max} values the response can be ranked as follows : 5 μl ocular spray > 5 μl instillate > 25 μl instillate.

Instillates are normally administered directly into the conjunctival sac with reflex blinking distributing the majority of the solution over the cornea. Even with small volume instillates, a substantial proportion of the solution is still emptied directly into the nasolacrimal drainage system. In using dosage forms of the invention targeted directly at the cornea our results showed that the solution uniformly covered the cornea with minimal splash-back upon impact, with a gradual pooling of liquid towards the conjunctival sac. Blinking in these instances distributed the solution over the corneal surface even further. This comparative study clearly shows that small volume ophthalmic solutions delivered in a droplet stream enhanced the bioavailability of ephedrine in comparison to the instillate presented from many commercial eyedroppers. A similar effect would be expected using other ophthalmic drugs.

Devices suitable for delivering dosage forms in accordance with the present invention are described in our International Patent Application Nos. GB95/01482 and GB95/02040, to which reference is directed.

CLAIMS

1. A dosage form useful in ophthalmic treatment comprising a stream of droplets of treatment fluid, each droplet having an ophthalmologically active compound in suspension or solution.

2. A dosage form according to Claim 1 wherein each droplet has the active compound in aqueous suspension or solution.

3. A dosage form according to Claim 1 or Claim 2 wherein each droplet is of a size sufficient to sustain its momentum in transmission from a delivery device to a target site.

4. A dosage form according to Claim 3 wherein each droplet is of a size sufficient to sustain momentum along a substantially horizontal path 5 cms in length from a discharge velocity of 5 to 25 m/sec from the delivery device.

5. A dosage form according to any preceding Claim wherein each droplet has a diameter in the range 100 to 800 μm.

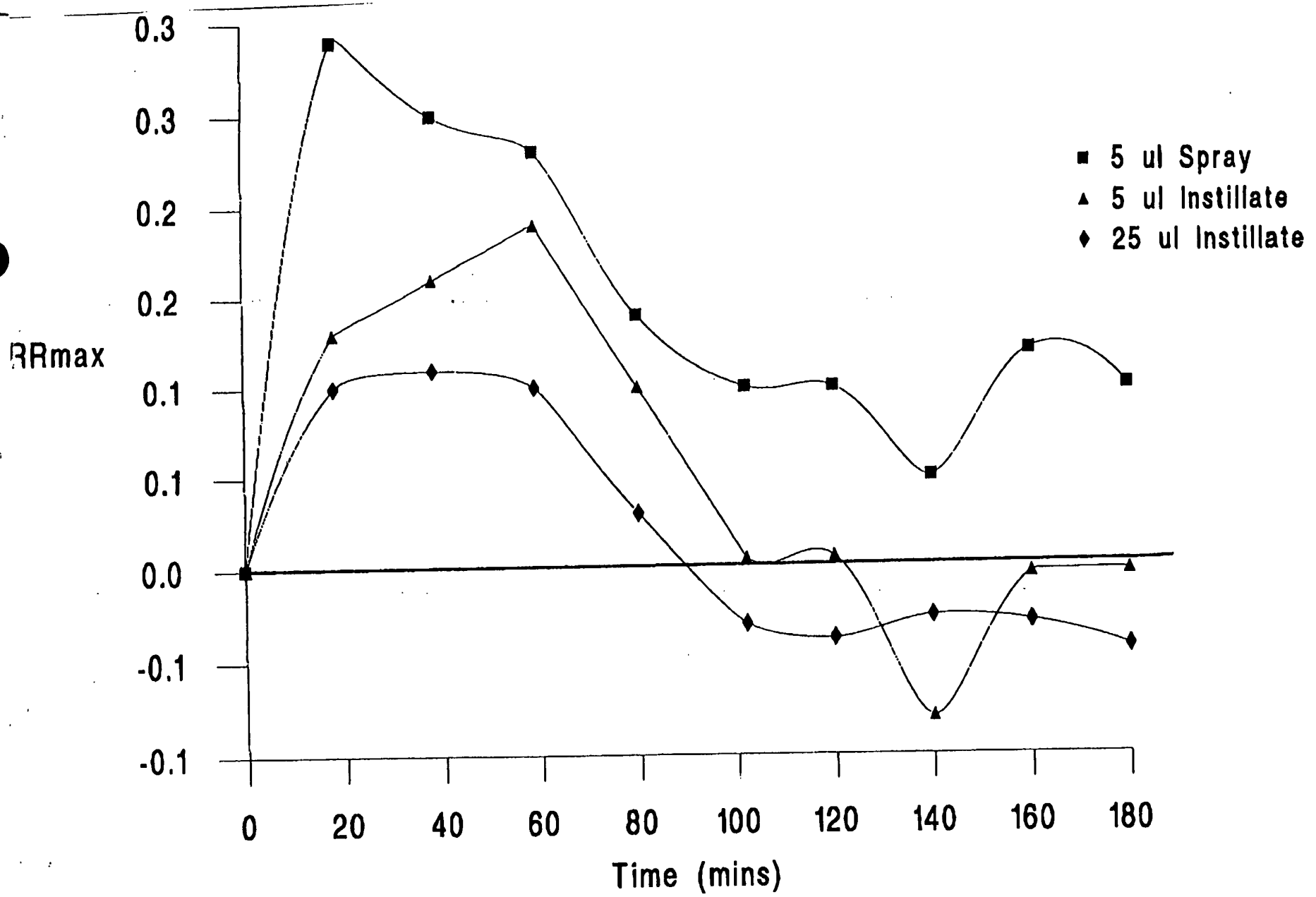
6. A dosage form according to Claim 5 wherein each droplet has a diameter in the range 200 to 400 μm.

7. A dosage form according to any preceding Claim in which the total volume of treatment fluid does not exceed 10 μl.

8. A dosage form according to Claim 7 in which the total volume of treatment fluid is in the range 3 to 8 μl.

9. A method of ophthalmic treatment comprising delivering to an eye a dosage form according to any preceding Claim.

10. A method according to Claim 9 wherein the eye is a human eye.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